REMARKS/ARGUMENTS

Claims 2-21 are currently pending in the above-identified application. In view of the remarks set forth below, reconsideration of all pending claims is respectfully requested.

Priority

Attached herewith are certified English translations of the foreign priority documents, Japanese Patent Application Nos. JP Hei 11-264679 and JP 2000-201456.

Rejections under 35 U.S.C. § 102

Claims 2, 4-8, 10-17, 20, and 21 remain rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Vito *et al.* The Examiner states that Applicant's position that a library of expressed nucleic acids as disclosed by Vito would not be the same as a library of expressed nucleic acids as recited in the present claims is unsubstantiated. (*See* Office Action dated December 14, 2005, at p. 9.) The Examiner further contends that "if several or even a few of the nucleic acids expressed in Vito are the same as those of the presently claimed invention ..., then the nucleic acids of Vito read on the present claims." (*Id.* at 10.) Applicant maintains traversal of the instant rejection as set forth below.

For a reference to anticipate a claim under 35 U.S.C. § 102, the reference must expressly or inherently disclose each and every limitation recited in the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); *see also* MPEP § 2106(II). Therefore, the reference must disclose the "identical invention ... in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Furthermore, consistent with the Examiner's obligation to consider every limitation in the claim, the Examiner "may not dissect a claimed invention into discrete elements in isolation." MPEP § 2106(II). The claim as a whole must be considered. *Id.*

In the present case, the claims recite "a library of nucleic acids ..." obtained from a particular source (namely, from "a tissue of an organism suffering from a disorder, wherein said tissue is obtained from an organ showing cell death as a pathological feature of the disorder") (emphasis provided). Accordingly, in view of the legal standard for anticipation as set forth above, the Examiner must consider the express limitation "library" of nucleic acids. The question is not whether "several or even a few" of the nucleic acids of Vito's cDNA library are the same as those contained in a library as recited in the claims. Instead, the question is whether Vito's cDNA "library of nucleic acids" itself, considered as a whole, is the same as that recited in the claims. By stating that only a few of the nucleic acids in Vito's library is sufficient to anticipate the claims, the Examiner has failed to consider the recitation of a "library" of nucleic acids derived from the specified source and, furthermore, has effectively "dissected" out the limitation "nucleic acid having a suppressive effect" into a discrete element in isolation of the claim as a whole, which, as set forth above, is prohibited by the MPEP and the Federal Circuit.

Secondly, with regard to whether Applicant has substantiated a difference between Vito's cDNA library and a nucleic acid library as recited in the claims, it is noted that Applicant previously submitted Ayroldi *et al.* (*Blood* 86:2672-2678, 1995) as evidence that, under physiological conditions *in vivo*, several other factors modulate apoptotic death of T lymphocytes (including, *e.g.*, interleukins and glucocorticoid hormones) as compared to the conditions used for stimulation of apoptosis of 3DO cells in Vito *et al.* (*i.e.*, stimulation with an anti-CD3ε 2C11 antibody *in vitro*). In view of Applicant's previous submission of Ayroldi *et al.*, and in view of the common knowledge in the art that differences between *in vitro* and *in vivo* culture conditions results in differences in gene expression, Applicant believes that a difference between Vito's cDNA library and a library as recited in the claims to be substantiated by the previous response.

With particular regard to the Examiner's view that the present claims contain "a product-by-process claim embedded in them," Applicant notes that the structure implied by the process steps are to be considered when assessing patentability over the cited art, especially where, for example, the "process steps would be expected to impart distinctive structural

characteristics to the final product." MPEP § 2113 (citing *In re Garneo*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)). As indicated above, in light of the common knowledge in the art, the process of obtaining libraries from cells grown under different conditions, particularly *in vitro* vs. *in vivo* conditions, would be expected to yield libraries with distinctive differences in relative abundances of particular sequences represented.

Nevertheless, to expedite prosecution of the instant application, Applicant submits herewith the Declaration of Dr. Masaaki Matsuoka under 37 C.F.R. § 1.132 (hereinafter the "Matsuoka Declaration"), together with supporting Exhibits A-C. The Matsuoka Declaration also makes reference to supporting Exhibits 1-3, previously submitted with Applicants Amendment of 9/21/05. The Matsuoka Declaration and supporting Exhibits show that the cDNA library of Vito *et al.* is different from a nucleic acid library as recited in the present claims, and would be viewed as such by a person of ordinary skill in the art.

As set forth in the Matsuoka Declaration, it is well-understood in the art that the nature of a nucleic acid expression library is not solely dependent on the chemical nature of one or a few nucleic acids in the library. (Matsuoka Declaration, ¶4.) Instead, the nature of a nucleic acid expression library depends on the totality of (1) the identity of all sequences represented in the library as well as (2) the frequency with which each of these sequences is present in the library. It is also well-understood that the identity and frequency of nucleic acids in an expression library depends on the expression levels of genes in the tissue or cells from which the library is derived. (*Id.*)

This understanding in the art, as summarized above, is shown by the way researchers in the field select and use mRNA sources for constructing libraries. (Matsuoka Declaration, ¶5.) Researchers generally choose an mRNA source where a target gene is expressed as highly as possible. In certain procedures, researchers use the "subtraction cloning method," which takes particular advantage of the difference in the expression level of specific genes between different tissue sources. Using this method, researchers effectively "erase" cDNAs commonly expressed in two tissue sources by subtraction with a DNA hybridization

procedure, yielding a subtracted cDNA library containing cDNAs whose original mRNAs are uniquely or more highly expressed in tissues or cells displaying particular phenotypic characteristics or subjected to particular conditions. The selection of particular mRNA sources and the use of the subtractive cloning method demonstrate the recognition in the art that (a) relative abundances of nucleic acids constitute structural features by which nucleic acid libraries are characterized and distinguished from each other and (b) differences in relative abundances of nucleic acids are particularly significant in the context of gene identification and cloning. (*Id.*)

As an exemplary demonstration of the way researchers select and use mRNA sources for constructing libraries, as discussed above, Ohira *et al.* (*J. Dent. Res.* 83:546-551, 2004) is attached hereto as evidentiary Exhibit B. Ohira *et al.* describes the use of subtractive hybridization to identify genes differentially expressed in rat alveolar bone wound healing. (*See* Exhibit B; *see also* Matsuoka Declaration, ¶6.) For identification of these genes, Ohira *et al.* selected injured peridontium tissue. The conclusion that injured peridontium cDNA was suitable for cloning of unique genes involved in wound healing stemmed from the observation that six known genes showed changes in mRNA expression levels relative to control tissue and histological changes were present in the injured tissue. (*See* Exhibit B at p. 548, second col., second full paragraph; *see also* Matsuoka Declaration, ¶6.) Thus, changes in expression levels of just a few genes and an observed phenotypic difference in a tissue source was sufficient to conclude that the injured peridontium cDNA library, as a whole, was <u>different</u> from the "driver" control cDNA used in the subtractive cloning method. (*Id.*)

Consistent with the knowledge in the art as discussed above, it is also well-known that culturing cells *in vitro* has effects on gene expression relative to cells grown more physiologically relevant conditions. (Matsuoka Declaration, ¶7.) It is particularly well-known that homogenous populations of cells cultured *in vitro*, especially immortalized cell lines, do not entirely replicate the physiological conditions or gene expression patterns of cells *in vivo*. (*Id.*) Sandberg and Ernberg (*Genome Biol.* 6:R65, 2005, also herein "Sandberg") is attached hereto as evidentiary Exhibit C to show this knowledge in the art. Sandberg states that cell lines "only

approximate the properties of *in vivo* cells in tissues," and that cell lines "have been selected under *in vitro* conditions for long periods of time, affecting many specific cellular pathways and processes." (Exhibit C, Abstract; *see also* Matsuoka Declaration, ¶7.) Sandberg goes on to state that the "use of immortalized cell lines as model systems of normal and pathological tissues is controversial"; that there are "obvious general differences between the environment of cells growing *in vitro* and that of *in vivo* tissue cells"; and that these differences "influence the gene expression and the phenotype of the cells grown *in vitro*." (Exhibit C at p. R65.10, second col.; *see also* Matsuoka Declaration, ¶7.) Sandberg's study shows that of approximately 7,000 genes investigated, approximately 30% showed statistically significant differential expression as compared to tissues. (Exhibit C at, *e.g.*, Abstract and p R65.2, second col.; *see also* Matsuoka Declaration.)

In view of the above, the process of constructing nucleic acid libraries from tissues of different origin or grown under different conditions would be expected to produce libraries with distinctive structural characteristics with respect to identity and relative abundances of sequences represented. (Matsuoka Declaration, ¶8.)

With regard to the Examiner's statement that if several or even a few of the nucleic acid expressed in Vito's library "are the same as those of the presently claimed invention ..., then the nucleic acids of Vito read on the present claims" (Office Action dated December 14, 2005, at p. 10), this statement is not consistent the common knowledge in the art regarding nucleic acid libraries as summarized above. (Matsuoka Declaration, ¶9.) The Examiner's statement does not take into account the frequency of expressed sequences, which, as set forth above, is a distinguishing structural feature of nucleic acid libraries. In fact, to the extent the Examiner's statement suggests that the frequency of expressed sequences does not affect the nature of a nucleic acid library, the Examiner directly contradicts the common knowledge in the art. (*Id.*)

The Examiner's statements also appear to ignore the effect of the conditions used in Vito *et al.* for inducing apoptosis in 3DO cells, as compared to conditions that would be

encountered physiologically *in vivo*, on a nucleic acid library. (Matsuoka Declaration, ¶10, citing Office Action dated December 14, 2005, at p.10.) In particular, with respect to the Examiner's assertion that the "conditions within which the cells were found upon obtaining or synthesizing the nucleic acids does not change the chemical nature of the expressed nucleic acids," this assertion again does not address the common knowledge in the art that the frequency of expressed sequences is a distinguishing structural feature of nucleic acid libraries; and further fails to take into account that conditions under which cells are grown, including *in vitro* conditions for culturing cell lines, have significant effects on gene expression as compared to gene expression in tissues *in vivo*. (Matsuoka Declaration, ¶10.)

In view of the common knowledge in the art as summarized in the Matsuoka Declaration, and in further view of the disclosure of Vito *et al.*, Vito's cDNA library is not the same as a nucleic acid library as recited in the claims of the '699 application (*i.e.*, is not the same as a library "obtained from or synthesized from nucleic acids expressed in a tissue of an organism suffering from a disorder, wherein said tissue is obtained from an organ showing cell death as a pathological feature of the disorder"). (Matsuoka Declaration, ¶11.) Vito discloses the expression of a cDNA library constructed from mRNA of an *in vitro* cultured cell line artificially stimulated using an antibody specific for CD3ε. Vito used a single cell species, 3DO, which is an immortalized hybridoma formed by the fusion of a mouse T cell with a thymoma cell (*see* Ashwell *et al.*, *J. Exp. Med.* 165:173, 1987, at page 174, last paragraph (Exhibit 1), cited by Vito in item 3 of "References and Notes"). As set forth in the Matsuoka Declaration and (*see* ¶7) and further evidenced by Sandberg (*see* Exhibit C), it is well-known in the art that homogenous populations of cells cultured *in vitro*, particularly immortalized cell lines, do not entirely replicate the physiological conditions or gene expression patterns of cells *in vivo*. (Matsuoka Declaration, ¶11.) As stated by Sandberg, there are "obvious general differences between the environment of cells growing *in vitro* and that of *in vivo* tissue cells"; and these differences "influence the gene expression and the phenotype of the cells grown *in vitro*." (Exhibit C at p. R65.10; see also Matsuoka Declaration, ¶¶7 & 11.) Therefore, a skilled person would readily understand that the *in vivo* gene expression patterns of a tissue obtained from a diseased organ

would differ from gene expression patterns of *in vitro* cultured 3DO cells. (*Id.* at ¶11.) Consequently, a library of nucleic acids obtained from or synthesized from nucleic acids expressed *in vivo* in a tissue obtained from a diseased organ would be different from Vito's cDNA library derived from *in vitro* 3DO cells.

With specific regard to the Examiner's statement that the nucleic acids of Vito were "obtained from cells undergoing PCD," the conditions used in Vito for inducing apoptosis in 3DO cells are not substantially representative of conditions that would be encountered physiologically. (Matsuoka Declaration, ¶12.) As noted above, the 3DO cells of Vito were stimulated with anti-CD3ε 2C11 antibody (an antibody specific for a particular subunit of the T cell receptor). However, under physiological conditions *in vivo*, T lymphocytes encounter several other apoptosis-modulating factors, including, *e.g.*, interleukins, glucocorticoid hormones, and adhesion receptors. (*See, e.g.*, Ayroldi *et al.*, *Blood* 86:2672-2678, 1995, at pp. 2672 and 2677 (Exhibit 2); *see also* Matsuoka Declaration, ¶12.) These other factors are capable of inducing specific positive (antiapoptotic and/or proliferative) and/or negative (apoptotic) pathways in lymphocytes. (*See* Exhibit 2 at, *e.g.*, p. 2672, first column; *see also* Matsuoka Declaration, ¶12.) Cells showing such differences in activation of apoptotic and survival pathways would be expected to show differences in gene expression patterns. (*Id.*) Therefore, for these reasons in addition to the reasons above, the cDNA library of Vito, constructed from a homogenous culture of 3DO cells stimulated using an anti-CD3 antibody but without the presence of other apoptosis-modulating factors found in more physiologically relevant conditions, is not the same as a nucleic acid library recited in the present claims, which require a source tissue "obtained from an organ showing cell death as a pathological feature of a disorder." (Matsuoka Declaration, ¶12.)

As indicated in Applicant's previous response, the presence of additional, more physiologically relevant factors *in vivo* that modulate cell death is of particular relevance to the invention claimed in the '699 application. (*See* Amendment filed September 21, 2005, at p. 9; *see also* Matsuoka Declaration, ¶13.) The '699 application provides the inventive insight that, in disorders accompanying cell death, cell death does not always occur in all cells contained in the

affected areas, and that tissues in the vicinity of the affected area may sufficiently express suppressor genes preventing the development of physiological symptoms. (*See* '699 application at, *e.g.*, p. 3, l. 18, bridging to p. 4, l. 5.; *see also* Matsuoka Declaration, ¶13.) The '699 application teaches, *inter alia*, that by using these tissues to construct a nucleic acid library, a library condensed for disease-suppressors can be obtained. (*Id.*)

With respect to the Examiner's statement that there is nothing in the claims to indicate that the nucleic acids obtained from a diseased organ have any structural or functional variation from nucleic acids obtained from a normal organ, Applicant again notes that the structure implied by process steps in a claim are to be considered when assessing patentability over the cited art, including where, for example, the "process steps would be expected to impart distinctive structural characteristics to the final product." MPEP § 2113 (citing *In re Garneo*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)).

In the present case, a nucleic acid expression library obtained from the tissue of a diseased organ is comprised of an expressed gene population distinguishable from that obtained from normal tissue. (Matsuoka Declaration, ¶14.) Applicant previously submitted Tajima *et al.* (*Neuroscience Letters* 324:227-231, 2002) (Exhibit 3) as evidence regarding differences in gene expression between diseased and normal tissues (this reference was originally cited in response to the rejections in view of Guo *et al.* and Giambarella *et al.*, now withdrawn). Tajima *et al.* shows the expression profile of Humanin ("HN," a neuroprotective polypeptide described in the Examples of the '699 application) in an Alzheimer's disease (AD) brain. Tajima *et al.* states the following:

> In an AD brain, HN immunoreactivity was detected in some of the intact large neurons in the occipital lobes (Fig. 3f). There was no similar immunostaining in neurons in an occipital lobe in an age-matched control brain (Fig. 3e). In the AD brain, HN immunoreactivity was also detected in small, round reactive glias (Fig. 3d, left panel). This type of immunoreactivity was widely distributed in the AD brain, most abundantly in the hippocampus. The age-

> matched control brain exhibited only few HN-immunoreactive glias (Fig. 3a).

(Tajima *et al.* at page 229, second col., last paragraph, bridging to page 230, first col.)

Based on the disclosure of the present application, together with variations in gene expression between diseased and normal tissue (*see* Matsuoka Declaration, ¶14) and the common knowledge in the art regarding the general nature of nucleic acid libraries (*see id.* at ¶¶4-8), a skilled artisan reading the claims would understand the recited nucleic acid library, which is "obtained from or synthesized from nucleic acids expressed in a tissue of an organism suffering from a disorder, wherein said tissue is obtained from an organ showing cell death as a pathological feature of the disorder," to be a library with the distinguishing structural feature of being condensed for disease-suppressor genes, relative to a library obtained from normal tissue. (Mastsuoka Declaration, ¶15.)

Claims 20 and 21. With particular regard to dependent claims 20 and 21, it is further noted that these claims specifically recite the step "obtaining the nucleic acids expressed in the tissue of the organism suffering from the disorder." This step is an express part of the method of claims 20 and 21 and cannot be construed as "product-by-process" limitations in a process claim. Because the Examiner has not shown where Vito discloses the step "obtaining the nucleic acids expressed in the tissue of the organism suffering from the disorder," claims 20 and 21 are novel over Vito *et al.*, in addition to the reasons set forth above.

For at least the reasons above as well as reasons previously of record, and in view of the evidence set forth herewith in the Matsuoka Declaration and supporting Exhibits, claims 2, 4-8, 10-17, 20, and 21 are novel over Vito *et al.* under 35 U.S.C. § 102(b). Withdrawal of the rejection is respectfully requested.

Claims rejections under 35 U.S.C. § 103

Claims 2, 4-8, 10-17, 18, 19, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Vito et al. in view of Slamon *et al.*

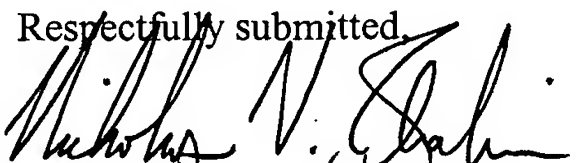
Applicants believe the present rejections to be obviated in view of the remarks set forth above, together with the Matsuoka Declaration and supporting Exhibits. In particular, a *prima facie* case of obviousness under 35 U.S.C. § 103 requires, *inter alia*, a teaching or suggestion of all claim limitations in the prior art. In this case, for the reasons previously set forth, the Examiner has not shown a teaching or suggestion in Vito *et al.* of "a library of nucleic acids obtained from or synthesized from nucleic acids expressed in a tissue of an organism suffering from a disorder, wherein said tissue is obtained from an organ showing cell death as a pathological feature of the disorder." Nor does Slamon address this deficiency in the art. Accordingly, withdrawal of the present rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,



Nicholas V. Sherbina
Reg. No. 54,443

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 206-467-9600
Fax: 415-576-0300
Attachments
NVS:seh
60685200 v1